Citation:

Ray JG, Vermeulen MJ, Boss SC, Cole DEC. Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada. *Can J Public Health.* 2002 Jul-Aug; 93 (4): 249-253.

PubMed ID: 12154524

Study Design:

Cross-sectional study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the changes in rates of folate and vitamin B_{12} insufficiency among Canadian adults after the mandatory folic acid food fortification program was implemented.

Inclusion Criteria:

- Data were obtained from samples collected by MDS Laboratories (a private lab that performs approximately 30% of folate and B_{12} testing in Ontario paid for by the universal health insurance plan)
- All consecutive, concomitant and non-redundant serum folate, RBC folate and Se B_{12} samples were analyzed
- Samples were collected for the following time periods:
  - Period A (April 1, 1997 to July 31, 1998)
  - Period B (August 1, 1998 to January 30, 1999)
  - Period C (February 1, 1999 to March 31, 2000).

Exclusion Criteria:

No exclusion criteria were specified.

Description of Study Protocol:

Recruitment

- Data were collected from MDS Laboratories for the time periods specified
- All consecutive, concomitant and non-redundant serum folate, RBC folate and Se B_{12} samples were analyzed.

Design

- This cross-sectional study analyzed data from individuals who underwent testing of their serum folate, red cell folate and serum vitamin B_{12} status during three time periods
- The time periods represent the pre-fortification period, a six-month interval spanning the lead and lag times for industry compliance and the post-fortification period
- Prevalence of serum folate, red cell folate, and serum B_{12} insufficiencies were compared between the three periods.

Dietary Intake/Dietary Assessment Methodology

No data were collected on dietary intakes.

Blinding Used

Patient confidentiality was maintained by removal of all patient identifiers.

Intervention

Folic acid fortification policy.

Statistical Analysis

- Distributions for all three measures were positively and significantly skewed; all values were log-transformed
- Geometric mean concentrations and 95% CIs were used to describe the data
- Quantile regression was used to estimate fifth percentile values and their 95% CIs
- An unpaired Student T-test was used to compare differences in mean concentration between periods A and C
- Prevalence rate ratios (RR) were used to compare insufficiency rates between periods A and C.

Cut-off Values Used to Define Insufficiency

Se folate insufficiency	Less than 3.4nmol per L
RBC folate insufficiency	Less than 215nmol per L

Se B_{12} insufficiency	Less than 120pmol per L
"Indeterminate" Se B_{12} insufficiency	Between 120 and 150pmol per L

Data Collection Summary:

Timing of Measurements

- Period A (April 1, 1997 to July 31, 1998)
- Period B (August 1, 1998 to January 30, 1999)
- Period C (February 1, 1999 to March 31, 2000).

Dependent Variables

Serum folate, red blood cell folate and serum B_{12} status.

Independent Variables

Level of folic acid fortification in Canada.

Control Variables

No other variables controlled for in this study.

Description of Actual Data Sample:

- *Initial N:* 8,884 consecutive, concomitant samples
- *Mean age:* 57.4 years (standard deviation 21.1 years)
- *Other relevant demographics:* 63.2% female
- *Anthropometrics:* No significant differences in distribution of age or sex between periods
- *Location:* Ontario, Canada.

Summary of Results:

Serum folate and red cell folate increased significantly from the pre-fortification period to the post-fortification period. No significant change was observed in serum B_{12} levels. See Table 1 for details.

Table 1: Folate and Vitamin B_{12} Levels in Ontario Before (Period A), During (Period B) and

After (Period C) Mandatory Folic Acid Fortification in Canada

Measure		Period A	Period B	Period C	Mean Absolute Change Between Period C vs. Period A
Serum Folate (nmol per L)	Mean (95% CI)	18.5 (18.1 to 18.9)	27.2 (26.5 to 27.9)	27.1 (26.8 to 27.5)	8.6 (P<0.001)
	Fifth percentile (95% CI)	6.3 (6.1 to 6.6)	10.1 (9.5 to 11.1)	10.9 (10.4 to 11.5)	
Red Cell Folate (nmol per L)	Mean (95% CI)	680.3 (668.8 to 691.9)	804.1 (787.4 to 821.1)	851.6 (841.2 to 862.0)	171.3 (P<0.001)
	Fifth percentile (95% CI)	297.0 (284.0 to 314.0)	405.0 (385.0 to 428.0)	450.0 (430.0 to 463.0)	
Serum B_{12} (pmol per L)	Mean (95% CI)	293.4 (288.0 to 298.8)	298.3 (290.3 to 306.4)	292.9 (288.3 to 297.6)	-0.5 (P=0.9)
	Fifth percentile (95% CI)	124.0 (122.0 to 129.0)	138.0 (129.0 to 145.0)	134.0 (129.0 to 140.0)	

Prevalence of folate insufficiency decreased significantly from Period A to Period C; no significant difference was observed for B_{12} insufficiency. See Table 2 for details.

Table 2: Prevalence of Normal and Abnormal Serum Folate, Red Cell Folate and Serum B_{12} Among Participants

		Period A (N, %)	Period B (N, %)	Period C (N, %)	Rate Ratio (95% CI) Period C vs. Period A
Serum Folate (nmol per L)	Less than 3.4 (deficient)	17 (0.52)	0 (0)	9 (0.22)	0.41 (0.18 to 0.93)
	3.4 or more	3,240 (99.48)	1,456 (100.0)	4,162 (99.78)	

Red Cell Folate (nmol per L)	Less than 215 (deficient)	57 (1.78)	8 (0.55)	17 (0.41)	0.23 (0.14 to 0.40)
	215 or more	3,143 (98.22)	1,442 (99.45)	4,085 (99.59)	
Serum B_{12} (pmol per L)	Less than 120 (deficient)	127 (3.93)	41 (2.78)	129 (3.11)	0.79 (0.62 to 1.01)
	120 to 150 (indeterminate)	153 (4.73)	67 (4.55)	193 (4.65)	0.98 (0.80 to 1.21)
	More than 150	2,953 (91.34)	1,365 (92.67)	3,825 (92.24)	

Other Findings

Among individuals with low B_{12} status (less than 150pmol per L), the rate of concomitant RBC folate insufficiency (less than 215nmol per L) decreased significantly from 0.38% in period A to 0.02% in period C (rate ratio 0.06, 95% CI 0.01 to 0.50).

Author Conclusion:

- A significant decline in folate insufficiency was observed during the post-fortification period in Canada; however, there was no decrease in vitamin B_{12} sufficiency
- These observations may have implications for the future detection of folate and B_{12} insufficiency as well as the need to consider recommendations for fortification or supplementation of vitamin B_{12}.

Reviewer Comments:

- *No information was available regarding disease status of the population studied*
- *All analyzed samples were collected from individuals who had undergone testing for folate and B_{12} status for undisclosed reasons, which may lead to a biased sample*
- *No information was available on dietary intakes or supplement use for this population.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes

2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	???
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???

3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	No

6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	???
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes

9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes